



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

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## Giardiasis (Last updated August 22, 2019; last reviewed August 22, 2019)

### Panel's Recommendations

#### I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of giardiasis?

- Giardiasis can be prevented by practicing good hygiene, not drinking or swimming in water that may be contaminated, and not eating food that may be contaminated (**expert opinion**).
- Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**).
- Initiating combination antiretroviral therapy (ART) in children with HIV infection to reverse or prevent severe immunodeficiency is the primary intervention to prevent severe enteric giardiasis (**strong, very low**).

#### II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat giardiasis?

- Tinidazole and nitazoxanide are preferred therapies; metronidazole is the alternative recommended treatment for giardiasis in children (**strong, moderate**).
- Dehydration and electrolyte abnormalities should be corrected (**expert opinion**).

#### III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of giardiasis?

- Recurrent episodes of giardiasis can be prevented by practicing good hygiene and avoiding contaminated food and water (**expert opinion**).
- Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**).

### Rating System

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; or Very Low

## Epidemiology

*Giardia duodenalis* (also known as *Giardia lamblia* or *Giardia intestinalis*) has a worldwide distribution, and giardiasis due to *G. duodenalis* is the most common nationally reportable intestinal parasitic disease identified by public health laboratories in the United States.<sup>1</sup> Giardiasis surveillance data show a bimodal age distribution, with the greatest number of reported cases occurring in children aged 1 to 9 years and adults aged 35 to 44 years. In the United States, most cases are reported between early summer and early fall and are associated with recreational water activities (e.g., swimming) and camping.<sup>1</sup>

Humans are the principal reservoir of *G. duodenalis*. The parasite is found in many animals species, although the role of zoonotic transmission is still being unraveled.<sup>2-4</sup> *G. duodenalis* is a flagellated protozoan with two forms: trophozoites and cysts. The infectious and environmentally resistant form is the cyst. After ingestion, each *Giardia* cyst produces two trophozoites in the proximal portion of the small intestine. Detached trophozoites pass through the intestinal tract, and form smooth, oval-shaped, thin-walled infectious cysts that are passed in feces. Duration of cyst excretion is usually self-limited but can vary and excretion may last for months. Studies in adults have shown that ingestion of as few as 10 to 100 fecally derived cysts is sufficient to initiate infection.<sup>5</sup> *Giardia* cysts are infectious immediately upon being excreted in feces and remain viable for at least 3 months in water at 4°C.<sup>6</sup> Although freezing will not eliminate the infectivity of *Giardia* cysts completely, heating, drying, or submersing them in seawater likely will.<sup>6,7</sup>

Infection with *Giardia* can occur directly by the fecal-oral route or indirectly via ingestion of contaminated water or food, but water contaminated with *Giardia* cysts appears to be the major reservoir and vehicle for spread of the parasite.<sup>1,8</sup> Most waterborne giardiasis outbreaks have been related to ingestion of untreated or improperly treated surface water.<sup>9,10</sup> Drinking untreated mountain stream water is a risk for hikers. Person-to-person spread of giardiasis occurs frequently in child care centers and in families of children with diarrhea.<sup>11-13</sup> Antigiardial host defenses are B-cell dependent, with secretory immunoglobulin A playing a major role in immunity. Individuals with humoral immunodeficiencies, such as X-linked agammaglobulinemia and hypogammaglobulinemia, who develop giardiasis are predisposed to chronic symptomatic disease.<sup>14</sup>

*G. duodenalis* infection is more common in certain high-risk groups, including children, employees and attendees of child care centers, patients and staff of institutions for people with developmental disabilities, men who have sex with men, people who ingest contaminated drinking water or recreational water (e.g., water from lakes, rivers, or inadequately treated swimming pools), travelers to disease-endemic areas of the world, close contacts of people with *Giardia*, people taking antibiotics,<sup>13</sup> and people exposed to *Giardia*-infected domestic and wild animals (e.g., dogs, cats, cattle, deer, and beavers).<sup>12,13,15</sup> There is little information on giardiasis in children with HIV infection, although *Giardia* has been associated with diarrhea in children with HIV infection and AIDS.<sup>16,17</sup> A recent study in Kenya described the association of enteric pathogens with HIV infection and HIV exposure in children. *Giardia* was the second most frequently associated pathogen, but the prevalence of *Giardia* was similar between the children with HIV and those exposed to HIV.<sup>18</sup>

Symptoms of giardiasis in individuals with HIV infection appear to be no more severe than in individuals who are HIV negative, and giardiasis is not typically considered a major cause of enteritis in patients with HIV.<sup>19</sup> There are no data in individuals with HIV but without advanced disease to suggest that the duration of parasite shedding or length of illness differs from that in individuals who are HIV negative. However, with progressive immunosuppression and reduced CD4 T-lymphocyte (CD4) cell counts, the risk of symptomatic *Giardia* infections increases. Studies in adults have demonstrated that enteritis due to *G. duodenalis* is a frequent event among patients with AIDS, especially in the most advanced stage of disease.<sup>20</sup> Research in adults with HIV infection from countries where giardiasis is endemic demonstrated that risk of *Giardia* infections and severity of disease increased with increasing immunosuppression and lower CD4 counts.<sup>21,22</sup> In a study of 75 adults with HIV infection in India, *G. duodenalis* was the most commonly isolated parasite, and patients with lower CD4 counts presented with significantly more enteric disease and chronic diarrhea.<sup>23</sup> In another study of 43 adults naive to combination antiretroviral therapy (ART), *G. duodenalis* was detected in one-third of patients and was significantly associated with lower CD4 counts (OR = 3.0 for CD4 counts  $\leq 100$  cells/mm<sup>3</sup>).<sup>24</sup> A cohort study comparing giardiasis in adults with HIV infection in Brazil before and after the introduction of ART demonstrates that the incidence of enteric diseases caused by *Giardia* decreased after ART was introduced.<sup>21</sup> Given the evidence, it is reasonable to recommend initiation of ART and immune reconstitution as a primary mode of *Giardia* prevention, which is consistent with standard practice to treat all children with HIV infection in the United States with ART.

## Clinical Manifestations

The *Giardia* incubation period usually lasts 1 to 2 weeks and averages 7 days.<sup>12</sup> Symptomatic infection with *G. duodenalis* can cause a broad spectrum of clinical manifestations. Children usually present with short-lasting, acute watery diarrhea with or without low-grade fever, nausea, anorexia, and abdominal pain. In others, the infection has a more protracted intermittent course, characterized by foul-smelling stools associated with flatulence, abdominal distension, and anorexia. Malabsorption combined with anorexia can lead to significant weight loss, failure to thrive, and malnutrition in children.<sup>25-27</sup> Stools can initially be profuse and watery and later become greasy and foul smelling. Blood, mucus, and fecal leukocytes are absent. Varying degrees of malabsorption can occur, and abnormal stool patterns can alternate with periods of constipation and normal bowel movements. Post-*Giardia* infection lactose intolerance can occur in 20% to 40% of patients.<sup>28</sup> This syndrome may take several weeks to resolve and can contribute to malnutrition in children. Malnutrition and repeated episodes of *Giardia* infection in the first years of life have been associated with poor cognitive function in late childhood.<sup>29,30</sup> Additionally, a proportion of patients in whom *G. duodenalis* is diagnosed will also develop chronic GI symptoms such as post infections irritable bowel syndrome (PI-IBS).<sup>30</sup>

Asymptomatic *Giardia* infection is common.<sup>31</sup> Extraintestinal invasion can occur with trophozoites migrating into bile or pancreatic ducts. Extraintestinal manifestations were previously considered unusual, but recent evidence demonstrates that one third of patients will express long term extraintestinal symptoms, including ocular, muscular and metabolic complications.<sup>30</sup> Subsequent development of reactive arthritis has also been associated with giardiasis.<sup>32,33</sup>

## Diagnosis

Although diagnostic tests for *Giardia* infection have not been evaluated in children with HIV, the tests are expected to perform similarly as in other populations. A definitive diagnosis of *Giardia* infection is established by detection of *Giardia* trophozoites or cysts in stool specimens, duodenal fluid, or small-bowel tissue by microscopic examination using staining methods such as trichrome; direct fluorescent antibody (DFA) assays; detection of soluble stool antigens using enzyme immunoassays (EIA); or use of molecular techniques including polymerase chain reaction (PCR).<sup>34-36</sup> EIA or multiplex PCR testing is the currently recommended methodology based on assay performance.<sup>36</sup>

Identification of both trophozoites and cysts can be made on direct smears of concentrated specimens of stool. Appropriately conducted direct examination of stool establishes the diagnosis of *Giardia* in up to 70% of patients with a single examination and in 85% with a second examination. Identification of *Giardia* can be difficult because of intermittent excretion of cysts. Stool specimens should be examined within 1 hour after being passed. Trophozoites are more likely to be present in unformed stools because of rapid bowel transit time. Cysts, but not trophozoites, are stable outside the gastrointestinal (GI) tract.

When giardiasis is suspected, and stool specimens are negative, aspiration, biopsy, or both, of the duodenum or upper part of the jejunum should be performed. In a fresh specimen, trophozoites usually can be visualized on direct wet mount. Histologic evaluation of duodenal biopsy samples has low sensitivity for detecting infection, however, this diagnostic approach may be necessary in patients with clinical characteristics of *Giardia* infection but negative stool and duodenal fluid specimens. Cytology techniques such as brush cytology or examination of the formalin fixative from tissue samples enhance detection of *Giardia* over biopsy analysis alone.<sup>37</sup> The commercially available Entero-Test is an alternative method for obtaining duodenal fluid directly.<sup>38</sup>

Using polyclonal antisera or monoclonal antibodies against *Giardia*-specific antigens rather than direct microscopy has improved diagnostic testing for *Giardia*. Studies comparing EIA kits for detecting *Giardia* antigen in stool showed a sensitivity of 87% to 100% and a specificity of 100%. All fluorescent antibody tests had 100% sensitivity and specificity.<sup>39</sup> These rapid diagnostic tests can be positive before and after detection of organisms by microscopic examination. DFA and EIA were equally sensitive, and both were more sensitive than microscopy of permanently stained smears after concentration in formalin ethyl acetate.<sup>40</sup> Specific antibodies to *Giardia* have been detected and quantified by immunodiffusion, hemagglutination, immunofluorescence, and EIA, but a serologic test is not available commercially.

Commercially available multiplex PCR panels for the detection of GI pathogens, including *Giardia*, are now available. These tests are highly sensitive (92% to 100%) and specific (96.9% to 100%) and can detect multiple GI pathogens simultaneously.<sup>41-43</sup>

## Prevention Recommendations

### *Preventing Exposure*

Because *Giardia* organisms are most likely transferred from contaminated water or food, or by contact with an infected person or animal, avoidance of untreated water sources and hand washing with soap and water after exposure to potentially fecally contaminated material or contact with an infected person or animal are recommended. These recommendations are especially important in individuals with severe immunosuppression. A study in adults with HIV infection in the United States demonstrated the benefits of hand hygiene. In the intervention group, a regimen of intensive hand washing (hand washing after defecation, after cleaning infants who had defecated, before preparing food, before eating, and before and after sex) coupled with weekly reminder telephone calls regarding hand hygiene resulted in fewer *Giardia* infections.<sup>44</sup> Alcohol-based gels are ineffective against *Giardia* cysts and should not be used as a substitute for hand washing when exposure to *Giardia* is a concern.

In a hospital, standard precautions (i.e., use of gloves and hand washing after gloves are removed) should be

sufficient to prevent transmission of *Giardia* from a patient with the infection to a susceptible person with HIV.

Before traveling to areas where the water may be contaminated or the safety of drinking water doubtful, travelers, hikers, and campers should be advised of methods to make water safe for drinking. These measures include using bottled water, disinfecting water by heating it to a rolling boil for 1 minute, or using a filter that has been tested and rated to National Safety Foundation Standard 53 or Standard 58 for cyst and oocyst reduction. Waterborne outbreaks of giardiasis can be prevented with a combination of adequate filtration of water sources, chlorination, and maintenance of water distribution systems.<sup>1,9</sup> Travelers should also be advised of the potential for transmission of giardiasis during use of contaminated recreational water (e.g., lakes, rivers, inadequately treated swimming pools).

### ***Preventing First Episode of Disease***

No chemoprophylactic regimens are known to be effective in preventing giardiasis. However, because the risk of acquisition of giardiasis and the severity of infection increase with the severity of immunosuppression, ART to prevent or reverse severe immunodeficiency is a primary modality for giardiasis prevention in children with HIV. In the United States, it is standard practice to treat all children with HIV infection with ART.

### ***Discontinuing Primary Prophylaxis***

Not applicable.

## **Treatment Recommendations**

### ***Treating Disease***

Effective ART and anti-parasitic therapy are the primary initial treatments for *Giardia* infections in children and adults with HIV infection.<sup>21</sup> Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation should be provided. Antimotility agents should be used with caution in young children. Patients with chronic diarrhea should be monitored for malabsorption leading to malnutrition.

The therapeutic efficacy of metronidazole against *Giardia* led to development of other nitroimidazole derivatives, such as tinidazole and secnidazole. These agents have the advantage of longer half-lives than metronidazole, making them suitable for single-daily-dose therapies. A single, 2-g dose (or the equivalent pediatric dosing of 50 mg/kg in a single dose) of tinidazole has demonstrated cure rates ranging from 80% to 100% and is also associated with improved medication adherence. Cure rates of patients with *Giardia* have been shown to be consistently higher with the use of tinidazole than with use of other anti-parasitic drugs such as metronidazole, nitazoxanide, mebendazole, albendazole and chloroquine.<sup>45-47</sup> Tinidazole is approved for use in children 3 years and older. The drug is available in tablets, which can be crushed in flavored syrup for patients unable to swallow tablets.

Nitazoxanide is approved in the United States for treatment of infections due to *G. duodenalis* in patients 1 year or older. A randomized, controlled clinical trial in adolescents and adults without HIV infection in Egypt demonstrated nitazoxanide's efficacy against placebo.<sup>48</sup> Nitazoxanide has been compared with metronidazole and mebendazole to treat giardiasis in children and was found to be equally effective, with eradication rates for *G. duodenalis* of 71% to 81% with nitazoxanide treatment.<sup>49</sup>

Metronidazole was determined to be therapeutic against giardiasis in 1962. Since then, clinicians have used metronidazole and other nitroimidazoles as the mainstay of therapy of giardiasis. Metronidazole is the drug most often used for giardiasis treatment worldwide. Children have been included in many of the clinical trials of metronidazole, with outcomes similar to those in adults (median efficacy, 94%) with 5- day to 10-day regimens.<sup>50</sup> Metronidazole is not available in a standard liquid form, but a suspension can be prepared by thoroughly crushing metronidazole tablets, using glycerin as a lubricant, and suspending the mixture in



flavored syrup.<sup>51</sup> Despite widespread and accepted use of metronidazole against *Giardia*, it has not been approved by the U.S. Food and Drug Administration for this indication.

Quinacrine has been used in combination therapy for cases in which treatment failure was suspected.<sup>52</sup> The severity of side effects prevented clinicians from using quinacrine as an initial therapeutic choice or first-line alternative, particularly in children. A bitter taste and vomiting led to the drug's lower efficacy in children, probably because of poor medication adherence.<sup>53</sup> Quinacrine is no longer available in the United States and has been discontinued by the manufacturer.<sup>54,55</sup>

### ***Monitoring and Adverse Events (Including IRIS)***

Patients with chronic diarrhea should be closely monitored for signs and symptoms of volume depletion, electrolyte and weight loss, and malnutrition. In severely ill patients, total parenteral nutrition may be indicated.

Adverse effects reported with tinidazole are not as common as with metronidazole but do include bitter taste, vertigo, and GI upset.<sup>50</sup>

Nitazoxanide is generally well tolerated with no significant adverse events noted in human trials. Adverse events have been mild and transient and principally related to the GI tract, such as abdominal pain, diarrhea, and nausea. Nitazoxanide has been well tolerated up to the maximum dose of 4 g when taken with or without food, but the frequency of GI side effects increases significantly with the dose level.<sup>49</sup>

The most common side effects of metronidazole treatment include headache, vertigo, nausea, and a metallic taste. Nausea occurs in 5% to 15% of patients given standard multiday courses. In addition, pancreatitis, central nervous system toxicity at high doses, and transient, reversible neutropenia have been attributed to metronidazole.<sup>50</sup>

Among patients taking quinacrine, 4% to 5% had yellow/orange discoloration of the skin, sclerae, and urine beginning about 1 week after starting treatment, and continuing up to 4 months after the drug was discontinued. Other common side effects of quinacrine included nausea, vomiting, headache, and dizziness. Quinacrine can precipitate hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals.<sup>53</sup>

Immune reconstitution inflammatory syndrome has not been associated with giardiasis or its treatment.

### ***Managing Treatment Failure***

The most important steps for management of giardiasis treatment failure are supportive treatment, optimal use of ART to achieve full virologic suppression, and modification of antiparasitic therapy. Treatment failures have been reported with all of the common anti-*Giardia* agents. It is important that clinicians differentiate between resistance to treatment and reinfection, which is common in *Giardia* endemic regions and situations where poor hygiene facilitates fecal-oral transmission. Resistance to most anti-*Giardia* agents has been documented, but there is no consistent correlation between *in vitro* resistance and clinical failure.<sup>50</sup> Clinically resistant strains have been treated with longer repeated courses or higher doses of the original agent or a drug from a different class to avoid potential cross-resistance. Using combination regimens that include metronidazole-albendazole, metronidazole-quinacrine, or other active drugs or giving a nitroimidazole plus quinacrine for at least 2 weeks have both proven successful against refractory infection. Combination therapy with albendazole-praziquantel, nitazoxanide-albendazole, and bacitracin-neomycin has been investigated in clinical trials. However, randomized controlled trials of combination therapy are limited and the optimal combinations need to be clarified, particularly in cases of treatment failure associated with suspected drug tolerance.<sup>56</sup> In patients with AIDS who have severe giardiasis, prolonged or combination therapy may be necessary.<sup>52,57</sup>

### ***Preventing Recurrence***

No known pharmacologic interventions effectively prevent recurrence of giardiasis. Reinfection is frequent in endemic areas, or in situations where hygiene is poor or contaminated water (e.g., in private wells) is not adequately treated. Reinfection can be prevented by consistently practicing good hand hygiene, but

particularly after defecation and handling of soiled diapers. Hand hygiene should also be practiced before preparing and eating food.<sup>12</sup> To reduce risk of disease transmission, children with diarrhea should be excluded from child care settings until the diarrhea has stopped. Children with giardiasis should not frequent recreational water venues for 2 weeks after symptoms resolve. Additional information about recreational water illnesses and how to stop them from spreading is available at <https://www.cdc.gov/healthywater/swimming/> and at <https://www.cdc.gov/parasites/giardia/prevention-control.html>.

### ***Discontinuing Secondary Prophylaxis***

Not applicable.

## **Recommendations**

### **I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of giardiasis?**

- Giardiasis can be prevented by practicing good hygiene, not drinking or swimming in water that may be contaminated, and not eating food that may be contaminated (**expert opinion**).

Because giardiasis results from ingestion of infectious cysts that are passed in the feces of infected individuals that may contaminate food or water, careful hand washing and washing of fruits and vegetables are recommended.

- Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**).

A randomized trial of an intensive hand washing intervention (i.e., handwashing after defecation, after cleaning infants who had defecated, before preparing food, before eating, and before and after sex) in 148 adults with HIV infection in the United States resulted in fewer episodes of diarrheal illness and *Giardia* infections during a one year period, demonstrating the effectiveness of hand washing.<sup>44</sup>

- Combination antiretroviral therapy of children with HIV infection to reverse or prevent severe immunodeficiency is the primary mode of prevention of severe enteric giardiasis (**strong, very low**).

A case-control study comparing giardiasis in adults with HIV infection in Brazil before and after the introduction of ART demonstrated that the incidence of enteric diseases caused by *Giardia* decreased after the introduction of ART.<sup>21</sup> Given the evidence, it is reasonable to recommend initiation of ART and immune reconstitution as a primary mode of giardiasis prevention.

### **II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat giardiasis?**

- Tinidazole and nitazoxanide are preferred, and metronidazole is the alternative recommended treatment for giardiasis in children (**strong, moderate**).

Clinical trials in children without HIV infection have demonstrated the efficacy of single dose tinidazole in comparison to other anti-parasitic drugs such as nitazoxanide, mebendazole, albendazole and chloroquine.<sup>45-47</sup> Tinidazole can be used in children 3 years and older. Nitazoxanide can be used in children 1 year or older. Metronidazole is inexpensive and widely available and has been used by clinicians as the mainstay of therapy of giardiasis. Metronidazole has been shown to be less efficacious than tinidazole, but comparable to nitazoxanide.<sup>7,45,58</sup>

- Dehydration and electrolyte abnormalities should be corrected (**expert opinion**).

There are no studies that address this specific management issue in giardiasis. However, recognition and management of hydration status and electrolyte imbalance are key to management of infectious diarrhea.

### III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of giardiasis?

- Recurrent episodes of giardiasis can be prevented by practicing good hygiene and avoiding contaminated food and water (**expert opinion**).
- Frequent hand washing can help reduce the incidence of diarrheal illnesses, including giardiasis (**strong, moderate**).

Good hygiene, including frequent hand washing and avoiding contaminated food and water, are recommended to prevent both initial and recurrent *Giardia* infections.

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### Dosing Recommendations for Prevention and Treatment of Giardiasis

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	ART to avoid advanced immunodeficiency	N/A	N/A
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	<p>Tinidazole 50 mg/kg orally, administered as one dose given with food (maximum dosage tinidazole 2 g). <b>Note:</b> Based on data from children who are HIV-negative.</p> <p><u>Nitazoxanide:</u></p> <ul style="list-style-type: none"><li>• Aged 1–3 Years: Nitazoxanide 100 mg by mouth every 12 hours with food for 3 days</li><li>• Aged 4–11 Years: Nitazoxanide 200 mg by mouth every 12 hours with food for 3 days</li><li>• Aged ≥12 Years: Nitazoxanide 500 mg by mouth every 12 hours with food for 3 days</li><li>• <b>Note:</b> Based on data from children who are HIV-negative</li></ul>	<p>Metronidazole 5 mg/kg by mouth every 8 hours for 5–7 days.</p> <p><b>Note:</b> Based on data from children who are HIV-negative.</p>	<p>Tinidazole is FDA-approved in the United States for children aged ≥3 years. It is available in tablets that can be crushed.</p> <p>Metronidazole has a high frequency of GI side effects. A pediatric suspension of metronidazole is not commercially available but can be compounded from tablets. Metronidazole is not FDA-approved for the treatment of giardiasis.</p> <p><u>Supportive Care:</u></p> <ul style="list-style-type: none"><li>• Hydration</li><li>• Correction of electrolyte abnormalities</li><li>• Nutritional support</li></ul> <p>Antimotility agents (e.g., loperamide) should be used with caution in young children.</p>

**Key:** ART = antiretroviral therapy; FDA = U.S. Food and Drug Administration; GI = gastrointestinal